DETAILED ACTION

Claims 1, 4-10, 12-19, 24-37, 39-51 are pending. Claims 1, 4, 5, 12, 13 are considered on the merits. Claims 6-10, 14-19, 24-37, 39-51 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

Claims 1, 4, 5, 12, 13 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There is little description of how to make the plasma preparation used in the method now under examination, which is itemized as (ii) in claim 1 and has been elected for examination. There is merely a general description of what might take place in the production of the plasma derived preparation.

Plasma is a complex liquid with many diverse proteins, including albumin, various globulins, α, β, ϒ, insulin, transferrin, enzymes, such as lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, hormones, smaller molecules such as ionic sodium, potassium, magnesium, phosphate, calcium, potassium, copper, iron, chloride, other small molecules such as glucose, amino acids, urea, bilirubin, uric acid and many other constituents. See Krebs [U2] where in 1950, around 100 components of native human plasma were known and quantitated.

The plasma preparation exemplified in Examples 9, 11 and 12 solution 4, is derived from plasma as the starting material and is also a complex liquid with, it is reasonable to assume, far more in it than the few components recited in the claims. This is because plasma, which is the starting material is extremely complex in composition.

In order for there to be sufficient written description and enabling disclosure of how to make a product, either a product composition must be completely described in terms of the chemical identity of each component and the concentrations thereof OR the process of making the product must be completely described. The complete description may be either in the specification or in another document which is referenced in the specification. Neither of these situations is present in the as filed specification.

The process for making the composition used in the claimed method is not sufficiently disclosed in the specification. The multiple steps which are suggested as preferences on page 27 and 28, are sparse guidance because they lack any detail for making the apparently novel plasma preparation used in a process of maintaining viable organs. For example, conditions for anion chromatography have not been disclosed, only that DEAE Sephadex should be used. It is to be noted that there seem to be more than one variety of DEAE Sephadex, A25 and A50, and that no conditions of elution, *i.e.* the eluting solvent, temperature, duration have been revealed. A subsequent treatment with Aerosil® is mentioned, but no conditions for this treatment have been revealed. There are many kinds of Aerosil®, 12 grades of hydrophilic fumed silica, 12 grades of hydrophobic fumed silica, 3 grades of fumed mixed oxides, more than 11 grades of hydrophobic silicas and hydrophobic metal oxides, etc., all of which are called Aerosil® see [U], catalog page for Aerosil®. No teaching of which one of these diverse products which are all called Aerosil® or how to use these products to obtain applicant's specific plasma derived product used in the examples is given in the specification. Ultrafiltration and diafiltration are mentioned as being performed, but no mention of what the solvent composition used in the process should be.

There is no citation in the specification to a published paper or a patent publication which details the making of this product. Thus, the product is apparently a novel one since there is no nexus to the disclosure of prior art publications.

Another manner in which the specification can be enabling is to describe the components of a composition in detail so that a synthetic composition might be compounded from its individual components. However, the product has not been sufficiently described in detail as to its components and the concentrations thereof. For example is there antithrombin III, complement C3 or transferrin in the product and at what concentrations are these components in the plasma preparation used in the method of perfusion treatments in examples 9, 11, and 12 solution 4. Since the starting material, plasma, contains these components and many more, it may be, but it is not certain that the final composition also contains these components as they have been removed during the undisclosed processing method of the native plasma.

In order for a complex product such as a plasma derivative to be used in a biological method of perfusing organs to preserve or repair them for their disclosed use in grafting and transplantation, the product and in the instant case, the making of the product from a complex natural source must be disclosed in sufficient detail in order to permit those of skill in the art to replicate the product and therefore successfully practice the exemplified methods of use of that product.

Preservation of organs, cells and tissues of sufficient quality for use in grafting/transplantation, which is the disclosed utility of the claimed invention is an art which to this date is not predictable. Many have tried to preserve organs with more or less success.

This field is highly unpredictable and still in early experimental stages, see review by El-Wahsh [V] which reviews progress to date in formulating preservation solutions for graft preservation of the liver. See the review by Steen [W] which reviews progress in preserving the endothelium during cardiovascular surgery.

If applicants have made an advance in this important and unpredictable medical field, it is incumbent upon them to fully disclose how they have made the advance in preservation solutions for organs. This they have not done.

An enabling description of how to make this apparently novel product, which is used in the perfusion method of the claims, is critical and is missing from the disclosure. It is still considered that the specification is fatally flawed in this respect. Lack of such disclosure also raises the issue of the sufficient disclosure of the best mode of practicing the invention.

Response to Arguments

Applicant's arguments filed 1/7/10 have been fully considered but they are not persuasive.

Applicants state that they can exclude disclosure of well known techniques and it is not undue experimentation for one of skill in the art to follow general teachings to obtain the described product used in the process. However, applicants fail to provide a published procedure or an issued patent or a published patent application which teaches how to make the composition used in the claims. Instead, they merely allege that given the scanty information in the specification, one of skill in the art could, for example, remove "toxic" lipids, without stating which lipids are toxic and are not present in the composition and which lipids are not toxic and therefore, are presumably in the preparation. The definition of toxic [V] is of, relating to, or caused by a poison or toxin.

The lipid profile of plasma is very complex and there are no lipids which are known to be "toxic". Lipids in plasma include the free fatty acids, such as palmitic, oleic, stearic, arachidonic and others, cholesterol, cholesterol esters such as cholesterol linoleate, palmitate, pamioleate, triglycerides which are an extremely complex set of lipids, phospholipids such as phosphotidylcholine, sphingomyelin, lysophophatidylcholine, phophatidylethanolamine and their variations depending on the identity and position of their fatty acid esters, see

Lehmann et al. [U]. Also lipids such as the vitamin E, vitamin D2, vitamin D3, vitamin A and esters thereof can be found. Applicant fails to indicate which of these is toxic and is therefore not present in the composition used in the claimed method.

The above is a small sample of the complexity of plasma and evidence of the lack of a complete written and enabling description of the product used in the examples of the specification.

Applicant argues that conditions and solvents and types of DEAE Sephadex or Aerosil is not critical not dispositive as all is known by others, but applicant continues to fail to provide any further information in the form of publications teaching the making of the presumably novel plasma preparation used in the claims. While it is well settled that a specification need not disclose what is well known in the art, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. There is a failure to meet the enablement requirement by not explaining the process that is required to make the complex product, which is argued to be novel by the applicants, used to exemplify the preservation method. That omission cannot be rectified by asserting that all the disclosure related to the process is within the skill of the artisan. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Applicant states on the record that the instant composition used in the examples is the composition sold under the trademark Biseko®. A publication which teaches in sufficient detail the process of making this trademarked substance would be sufficient to remove the enablement rejection. The disclosure of the use of a composition which is kept as a trade secret and which is essential to the practice of the invention does not fulfill applicants' duty to describe the invention in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains...to make and use the same.

INDEFINITE

Claims 1, 4, 5, 12, 13 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 uses the term "toxic lipids", but fails to state what these lipids are or how they are to be determined as toxic. Toxic is a term of comparison without any definition of what might be encompassed by this term.

Claim Rejections - 35 USC § 102/103

Claims 1, 4, 5, 12 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US 4,073,886 [A].

The claims are directed to a method of contacting an isolated hollow organ with a perfusion solution comprising:
a) physiological electrolyte solution,
b) a homologous, anti-coagulatory blood plasma preparation comprising human plasma proteins, anti-coagulatory acting factors and immunoglobulins from which the procoagulatory acting factors, isoagglutinins and lipoproteins and toxic lipids of the blood plasma have been removed,
c) a nutrient substrate.

The reference is relied upon as explained below.

US 4,073,886 disclose a treated plasma preparation for use as an organ (specifically mentioned kidney, heart, lung) perfusate where the coagulation factors have been removed. The plasma preparation is citrated and sterile, Example 1. A plasma derived preparation such as disclosed would be reasonably assumed to have physiological electrolytes and nutrients in it because plasma has these components.

With regard to the components recited in claim 4, all of these components are considered to be present in the compositions of the prior art references in the absence of evidence to the contrary, because they are all present in the starting material, plasma.

Likewise the concentrations of the components recited in claims 5, 12 are considered to be the same as or so close to, that in the absence of evidence to the contrary, they are not patentably distinguishable from the inherent concentrations of these substances in the cited prior art plasma preparations.

With regard to the differences in concentrations between the instant claims and the disclosure of the prior art, see MPEP 2144.05 I. and II.

Generally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation, *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 284 F.2d 955 (CCPA 1960). MPEP 716.02(d).

With regard to the type of organ, *i.e.* specifically blood vessels and lymphatic vessels, the references both generically disclose that the plasma preparations disclosed in the references may be used to perfuse organs. The generic term "organs" includes all organs and therefore, encompasses blood vessels and lymphatic vessels. Therefore it would be obvious to employ the plasma preparations of the cited prior art for blood vessels, lymphatic vessels or any other organ in the absence of evidence of criticality.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over4,073,886 [A] as applied to claims 1, 4, 5, 12 above, and further in view of Dichtelmuller *et al*. [X].

The claims are further directed to the use of a β-propiolactone, UV treated plasma preparation.

Dichtelmuller *et al*. teach a process of treating plasma and plasma derivatives with β-propiolactone and UV irradiation in order to inactivate viruses present in the plasma or plasma derivative (Summary, p. 367)

One of ordinary skill in the art would have been motivated at the time of invention to make these additions in order to obtain the results as suggested by the references with a reasonable expectation of success. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Response to Arguments

Applicant's arguments filed 1/7/10 have been fully considered but they are not persuasive.

Applicant argues that the composition of US '866 fails to teach the removal of the noted components while leaving the remaining native components intact. Removal of noted components is interpreted to mean removal of pro-coagulatory factors, isoagglutinins, lipoproteins and toxic lipids.

The composition is disclosed to have removed the lipoproteins, lipids and the coagulatory factors, see Example 1, and col. 1, l. 67. With regard to the removal of isoagglutinins, the reference is silent. However, the use of a step of cryoprecipitation, which is also applicants first step combined with the tricalcium phosphate adsorption step and the Pluronic F-38 precipitation step is considered to have removed the isoagglutinins to at least the same degree as

the commercial preparation Biseko® used in the exemplification in the absence of evidence to the contrary.

While it is uncertain what the phrase "remaining native components intact" means, it is interpreted to mean that the composition retains plasma proteins, anti-coagulatory-acting factors, immunoglobulins present in native plasma. In the absence of evidence to the contrary, the composition of the reference is assumed to retain these components at least to the extent that they are present in the commercial preparation Biseko®.

Applicants argue that the combination of a nutrient substrate, and a physiological electrolyte solution with the plasma derivative is not disclosed in US '886. Please look at example I, where sodium chloride is added to dissolve the precipitate from the Pluronic F-38 treatment. Since the subsequent steps all retain the supernatant and the saline, a physiological electrolyte solution is retained in the final composition. Also, sodium citrate is added prior to filtration. Citrate is a nutrient substrate. Also, the ions in the composition are all present in plasma and are considered to also be present in the plasma product since plasma is the starting material in the absence of evidence to the contrary, and thus, all elements of the claimed composition are in the composition of the cited prior art.

The Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' composition differs and, if so, to what extent from the compositions discussed in the reference. Accordingly, it has been established that the prior art composition, which has been obtained from plasma and shares the property of being able to be used in organ perfusion methods demonstrates a reasonable probability that it is either identical or sufficiently similar that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

Merely because a characteristic of a known composition is not disclosed in a reference does not make the claimed composition patentable. The disclosed composition possesses inherent characteristics which might not be displayed in the tests used the reference.

Applicant argues that the use of Biseko® in a method of perfusion of blood vessels yields unexpected advantages and present a paper by Weiss *et al.*, which compares the use of saline, saline plus 5% albumin, HTK solution, heparinized autologous blood and Biseko® in a method of perfusion of vein. However, this is not a comparison of the use of a plasma preparation of the cited prior art with the instant composition. Therefore, it is not persuasive. Likewise the papers by Szolnoky *et al.* and Juchem *et al.* are not comparisons with the cited prior art and do not overcome the obviousness rejection.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sandra Saucier/
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